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ความสัมพันธ์ระหว่างค่าสภาพการยอมให้น้ำผ่านและค่าความพรุน ของแผ่นฟิล์มยางธรรมชาติผสม

จิระพรชัย สุขเสรี, ประภาพร บุญมี, วิรัช ทวีปรีดา, กาญจน์พิมล ฤทธิเดช, วิวัฒน์ พิชญากร*

บทคัดย่อ

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บทนำ: เครื่องมือและเทคนิคหลายชนิดถูกพัฒนาขึ้นเพื่อใช้ประเมินสมบัติความพรุนของวัสดุต่างๆ อย่างไรก็ตาม การวัดค่าที่ถูกต้องของสมบัตินี้ในตัวอย่างรูปแบบฟิล์มเป็นไปได้ยาก งานวิจัยฉบับนี้มุ่งเน้นถึงการศึกษาความสัมพันธ์ระหว่างค่าสภาพการยอมให้น้ำผ่านและค่าความพรุนของแผ่นฟิล์มยางธรรมชาติผสมซึ่งถูกพัฒนาขึ้นเพื่อประยุกต์ใช้ในระบบนำส่งยาทางผิวหนัง **วัสดุและวิธีการทดลอง:** แผ่นฟิล์มพอลิเมอร์ผสมถูกเตรียมขึ้นจากน้ำยางธรรมชาติโปรตีนต่ำซึ่งเตรียมขึ้นใช้เอง และพอลิเมอร์ผสมที่ใช้คือ ไฮดรอกซีโพรพิลเมทิลเซลลูโลส, โซเดียมคาร์บอกซีเมทิลเซลลูโลส, เมทิลเซลลูโลส หรือพอลิไวนิลแอกอฮอล์ และใช้กลีเซอรีน หรือไดบิวทิลพทาเลต เป็นพลาสติไซเซอร์ มีการใช้นิโคตินเป็นตัวยาต้นแบบสำหรับเติมลงในแผ่นฟิล์มนี้ด้วย สามารถเตรียมแผ่นฟิล์มได้ง่ายโดยวิธีการเทลงในจานแก้วและทำให้แห้งที่อุณหภูมิ 70±2 องศาเซลเซียส เป็นเวลา 4 ชั่วโมง ค่าฟลักซ์น้ำของแผ่นฟิล์มถูกวัดโดยระบบการกรองแบบปลายปิด และคำนวณค่าสภาพการยอมให้น้ำผ่านจากความชันของความสัมพันธ์ระหว่างค่าฟลักซ์น้ำกับความดัน ในอีกวิธีหนึ่ง สามารถหาค่าความพรุนของแผ่นฟิล์มโดยเทคนิคการแช่ฟิล์มในน้ำกลั่น คำนวณหาค่าร้อยละของความพรุนจากความแตกต่างของน้ำหนักแผ่นฟิล์มที่เปียกและที่แห้งสนิท ค่าความพรุนจากทั้ง 2 เทคนิคที่ได้จากตำรับเดียวกันถูกเปรียบเทียบเพื่อหาความสัมพันธ์ **ผลการทดลอง:** การผสมพอลิเมอร์และพลาสติไซเซอร์หลายชนิดมีผลอย่างมีนัยสำคัญต่อการเพิ่มขึ้นของค่าสภาพการยอมให้น้ำผ่านและค่าความพรุนของแผ่นฟิล์มยางธรรมชาติผสม ขึ้นกับสมบัติความชอบน้ำและการละลายของพอลิเมอร์และพลาสติไซเซอร์ ยิ่งไปกว่านั้น นิโคตินซึ่งเป็นยาที่ละลายน้ำได้ก็มีผลทำให้สมบัติความพรุนของแผ่นฟิล์มที่บรรจุยานี้มีค่าเพิ่มมากขึ้นด้วย ซึ่งสังเกตได้จากค่าที่ได้จากการวัดทั้งสองวิธีเพิ่มขึ้น ปรากฏความสัมพันธ์ระหว่างค่าทั้งสองนี้ที่ได้จากการวัดโดยวิธีที่แตกต่างกัน โดยผลการทดลองให้ผลในแนวทางเดียวกัน อย่างไรก็ตาม การผสมพอลิเมอร์ พลาสติไซเซอร์ และนิโคติน มีผลต่อค่าที่ได้เนื่องจากคุณสมบัติที่แตกต่างของสารเหล่านี้ ค่าร้อยละของความพรุนซึ่งคำนวณได้จากเทคนิคการแช่ฟิล์มนั้นให้ผลที่น่าเชื่อถือมากกว่าค่าสภาพการยอมให้น้ำผ่าน อย่างไรก็ตาม วิธีหลังสามารถทำได้ง่ายกว่าและใช้เวลาน้อยกว่าวิธีแรก คุณสมบัตินี้มีประโยชน์ต่อการทำนายอัตราการปลดปล่อยยาในระบบนำส่งยาทางผิวหนังในรูปแผ่นฟิล์ม **สรุปผลการทดลอง:** พบรูปแบบผลที่เหมือนกันในทั้งค่าสภาพการยอมให้น้ำผ่านและค่าร้อยละความพรุนที่แสดงถึงสมบัติความพรุนของแผ่นฟิล์มยางธรรมชาติผสม ดังนั้นสรุปได้ว่าค่าสภาพการยอมให้น้ำผ่านและค่าร้อยละความพรุนมีความสัมพันธ์กันโดยตรง แต่อย่างไรก็ตาม ทั้งสองค่านี้ต่างก็ได้รับผลกระทบจากส่วนประกอบที่เติมลงไปผสม ได้แก่ พอลิเมอร์ พลาสติไซเซอร์ และยาในแผ่นฟิล์ม

คำสำคัญ : แผ่นฟิล์มยางธรรมชาติผสม, ความพรุน, ค่าสภาพการยอมให้น้ำผ่าน, ระบบนำส่งยาทางผิวหนัง

Abstract

Relationships between Hydraulic Permeability and Porosity of Natural Rubber Blended Films
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Introduction: Several instruments and techniques had been developed to evaluate the porosity of materials. However, it is difficult to measure the exact value of this property in film samples. This research focused on the study of the relationships

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between hydraulic permeability and porosity values in natural rubber blended films which be developed for transdermal delivery applications. **Materials and method:** The natural rubber blended films were prepared from deproteinized natural rubber latex (DNRL) which was developed in-house, a blended polymer was hydroxypropylmethyl cellulose (HPMC), sodium carboxymethyl cellulose (SCMC), methylcellulose (MC), or polyvinyl alcohol (PVA), and glycerine or dibutylphthalate was used as a plasticizer. Nicotine was added in the filmformulation as a model drug. The films were constructed by simple pouring in the Petri-dish and dried in hot air over at 70±2 °C for 4 hours. The water flux values of films were measured by using dead-end stirred cell. The hydraulic permeability was calculated from the slope of water flux value versus pressure. In the other hands, the porosity of films was determined by immersing technique in distilled water. The percentage of porosity was calculated from different weights of wet and dry state of films. The values of both techniques obtained from the identified formulations were compared to find the relationships. **Results:** The blending of various polymers and plasticizers in DNRL significantly affected on increasing hydraulic permeability and porosity values in the natural rubber blended films depended on the hydrophilicity and solubility of polymers and plasticizers. Moreover, nicotine, which is water-soluble drug, also gave the higher porosity property in drug loaded films which indicated by the increasing of both values. There were the relationships between the values from both techniques. The results were in the same manner. However, the blended polymer types, plasticizer, and nicotine could also affect the measured values due to their different properties. The percentage of the porosity calculated by immersing technique was quite reliable than the hydraulic permeability. However, the latter technique was easier and took less time than the first one. This property was valuable for the prediction of drug release rate in transdermal drug delivery systems as film dosage forms. **Conclusions:** The similar result patterns were observed in both hydraulic permeability and percentage of porosity for indicating the porosity property in natural rubber blended films. Thus, hydraulic permeability and percentage of porosity were related. However, both values were affected by blended ingredients i.e., polymers, plasticizers, and drugs in films.

Keywords: Natural rubber blended films, Porosity, Hydraulic permeability, Transdermal delivery systems

Introduction

The membrane porosity plays an important role for drug diffusion and transport ways from transdermal drug delivery. Nowadays, several instruments and techniques had been developed to evaluate the porosity of materials. Laser scattering method, electrical sensing zone method, microscopy method, Brunauer, Emmett and Teller (BET) method (Brunauer *et. al.*, 1938), permeability, and x-ray diffractometry (XRD) technique could measure the void space in materials (Taylor *et. al.*, 1998). In these techniques, only BET method had been accepted and available for porosity determination. However, this method is appropriated for powder particles or materials which could be cut into smaller sizes. Unfortunately, it is difficult to measure the exact value of this property in film samples.

Transdermal drug delivery systems, also known as transdermal patches, are the polymeric films which be directly adhered on the skin. The drug molecules are released by dissolution and diffusion mechanisms from these films, and penetrated the skin into systemic blood circulation (Chien, 1992). Many small molecular drugs such as clonidine, estradiol, fentanyl, nicotine, nitroglycerin, oxybutynin, and scopolamine are available used in this system (Farahmand and Maibach, 2009). Moreover, many types of polymer are selected for film formation and controlling drug release and permeation.

Natural rubber latex (NRL) is a colloidal polymer that was tapped from *Hevea brasiliensis* or Para rubber tree. The NRL could be ease to film forming with good tensile properties, high elongation at break, and impermeability of gases and liquids (Roberts, 1998). However, the International Union of Immunological Societies (IUIS) reported the clearly known 14 NRL proteins (Hev. B1-14) as allergic agents of NRL (Raulf-Heimsoth *et. al.*, 2007, WHO/IUIS Allergen Standardization Committee, 1984). In this study, the natural rubber blended films were prepared from deproteinized natural rubber latex (DNRL) which was developed in-house, a blended polymer was hydroxypropylmethyl cellulose (HPMC), sodium carboxymethyl cellulose (SCMC), methylcellulose (MC), or polyvinyl alcohol (PVA), and glycerine or dibutylphthalate was used as a plasticizer. Nicotine was added in these films as a model drug. However, these natural rubber blended films were very sticky which could not be grinded into small size for porosity determination by BET method.

Two different techniques were selected to predict the porosity property in natural rubber blended films: (1) determining the hydraulic permeability by the distilled water filtration through the films (Gullinkala *et. al.*, 2010, Khan *et. al.*, 2010) and (2) calculating the percentage of porosity by immersing the films in distilled water (Chen *et. al.*, 2004). However, there is no report which summarized the relationship between the hydraulic permeability and the percentage of porosity of films. Both techniques should be compared and discussed. Thus, this research focused on the study of the relationships between the hydraulic permeability and the percentage of porosity values in natural rubber blended films which be developed for transdermal delivery applications.

Materials and methods

DNRL was prepared in-house by enzymatic process to remove the protein from fresh NRL. This DNRL could reduce the total protein content for more than 89.21% when compared with initial protein in NRL (Suksaeree *et. al.*, 2011). (-)-Nicotine (>99%) was purchased from Merck (Germany). HPMC (grade E5) was purchased from Onimax (Thailand). MC 4000 and SCMC 1500 were supplied from Srichand United Dispensary (Thailand). DBP was purchased from Fluka (USA.). GLY was supplied from P.C. drug center (Thailand).

Film preparations

The various blended polymers were dissolved in distilled water to obtain 10%HPMC, 2.5%SCMC, 2.5%MC or 10%PVA. Then, 10 phr of each polymer was mixed homogeneously into DNRL with or without 10 phr of plasticizer. In some formulations, nicotine aqueous solution was mixed as a model water-soluble drug. These mixtures were stored at 4ºC overnight to decrease the air bubbles and form a clear viscous solution. Then, the films were constructed by simple pouring in the Petri-dish and dried in hot air over at 70±2 °C for 4 hours. Subsequently, dry films were peeled from Petri-dish and kept in desiccators.

Hydraulic permeability determination

The water flux values of films were measured by using a laboratory-scale dead-end stirred cell filtration system (Fig. 1) (Chinpa, 2008) at room temperature. The operating pressure of 500 - 2,000 kPa was examined. The natural rubber blended films was cut into a circular shape with area of 10.76 cm^2, and placed into the cross-flow membrane modules. The water flux was determined as the distilled water filtration though the void space in the films. The compaction tests continued until a steady-state flux was obtained. The water flux values were calculated by volume of water filtration (V, L) per the operating time (t, h) per effective membrane area (A, m^2). The hydraulic permeability (L_P, m/s·Pa or m^3/N·s) was then determined from slope of water flux value (L/m^2·h) versus pressure (kPa) multiply with hydraulic permeability factor as following in Eq. (1) (Bhongsuwan and Bhongsuwan, 2008).

$$\text{Hydraulic permeability } (L_p) = \text{slope} \times 2.77 \times 10^{-10} \quad (1)$$

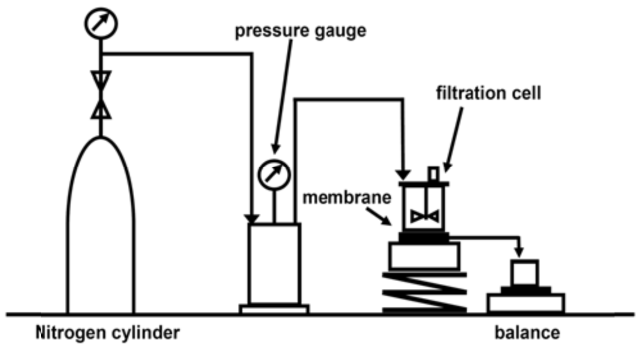

Fig. 1 Schematic diagram of a dead-end stirred cell filtration system (Chinpa, 2008)

Percentage of porosity determination

The films were cut into 1 X 1 cm^2 and dried in oven at 60±2ºC for overnight. The dry films were immersed in 5 ml distilled water at room temperature. The hydrated films were taken out, weighed until constant (W_w), and measured the wide, length and thickness. Then, they were dried at 60±2ºC for overnight and weighed again (W_d). The percentage of porosity was calculated by different weights of wet and dry state of films by Eq. (2).

$$\%Porosity = \frac{(W_w - W_d)}{d_{water}} \times \frac{100}{w \times l \times t} \qquad (2)$$

where W_w and W_d = the weights of the films in the wet and dry states (g), respectively; d_{water} = the density of pure water at 20°C; and w, l, t = the wide (cm), length (cm) and thickness (cm) of the films in the wet state, respectively (Chen *et. al.*, 2004).

Results and Discussion

The water flux of DNRL film and natural rubber blended films was presented in Fig. 2 and 3, respectively. The hydraulic permeability was further calculated and shown in Fig. 4(A). It was found that the hydraulic permeability of films depended on film properties. DNRL film without polymer blends showed the low hydraulic permeability because it was hydrophobic film without visible pores when observed by simple microscope and high resolution scanning electron microscope (SEM) (data not shown). The blending of various polymers and plasticizers in DNRL significantly affected on increasing hydraulic permeability in the natural rubber blended films depended on the hydrophilicity and solubility of polymers and plasticizers. This result was related with previous study (Siepmann and Peppas, 2001). From these results, the hydrophilicity and solubility of polymers were in the range of HPMC<PVA<SCMC<MC, and those of plasticizers were ranged in the range of DBP<GLY. Moreover, nicotine which is water-soluble drug also gave the higher hydraulic permeability in drug loaded. These results indicated that the soluble ingredients could dissolve in hydraulic permeability determination process, resulting in more pores. Thus, this technique could predict the porosity properties in these polymeric films.

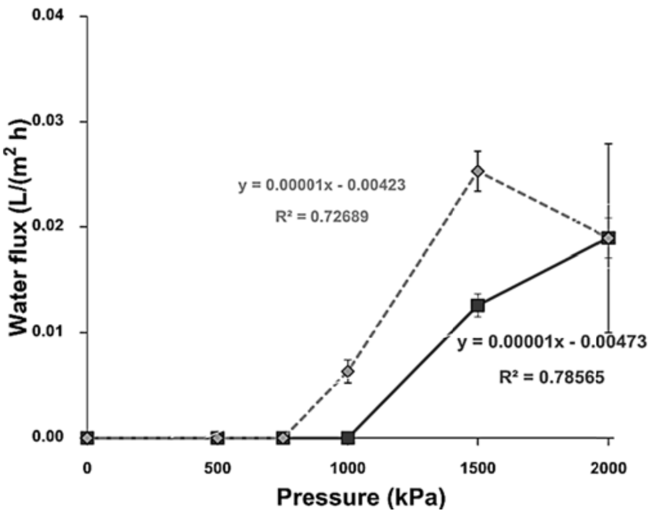

Fig. 2 Water flux values of DNRL films (red square) without and (blue diamond) with nicotine loading.

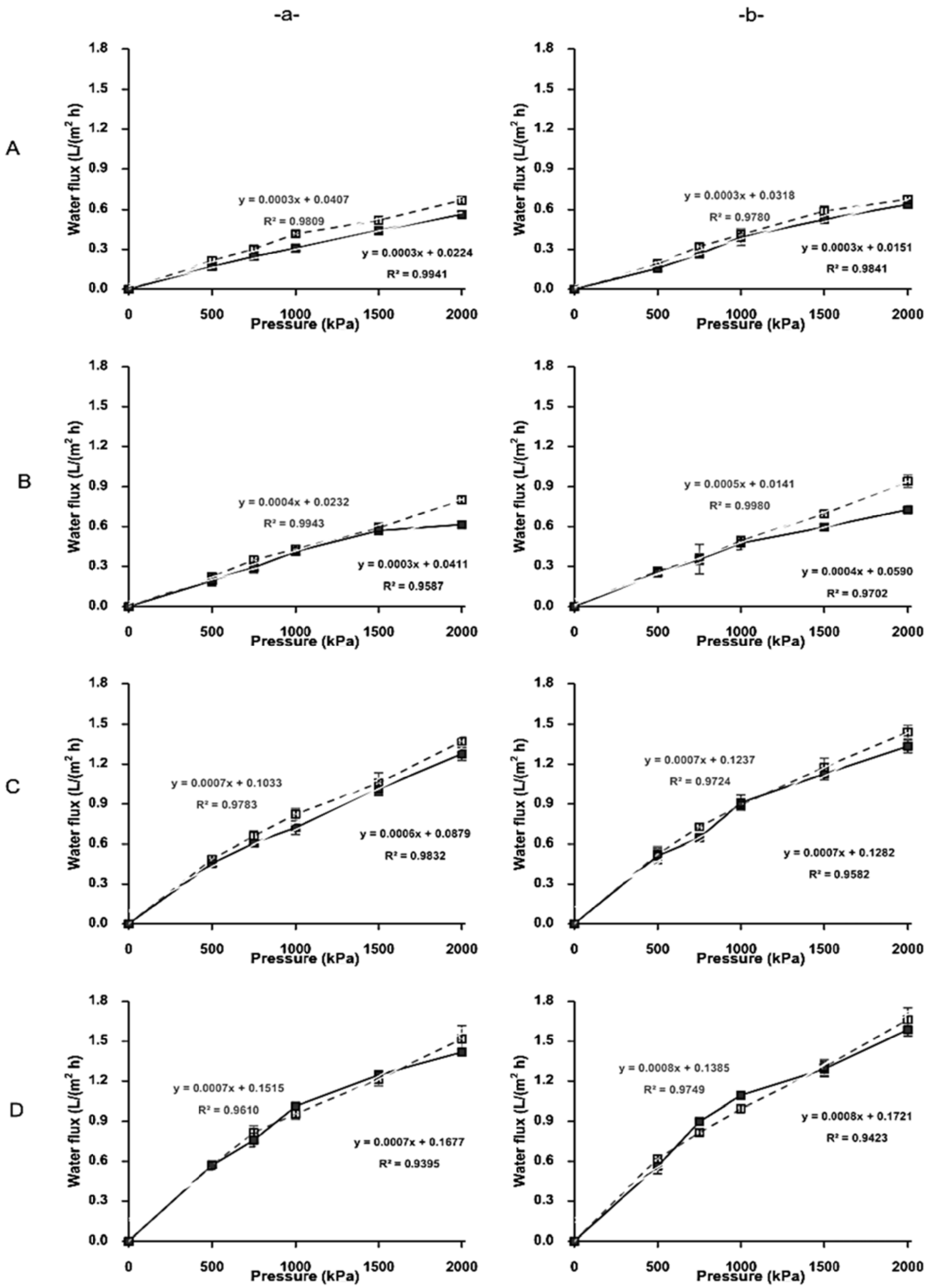

Fig. 3 Effects of (A) HPMC, (B) PVA, (C) SCMC or (D) MC with (-a-) DBP or (-b-) GLY on the water flux values of natural rubber blended films (—■—) without and (- -□- -) with nicotine loading.

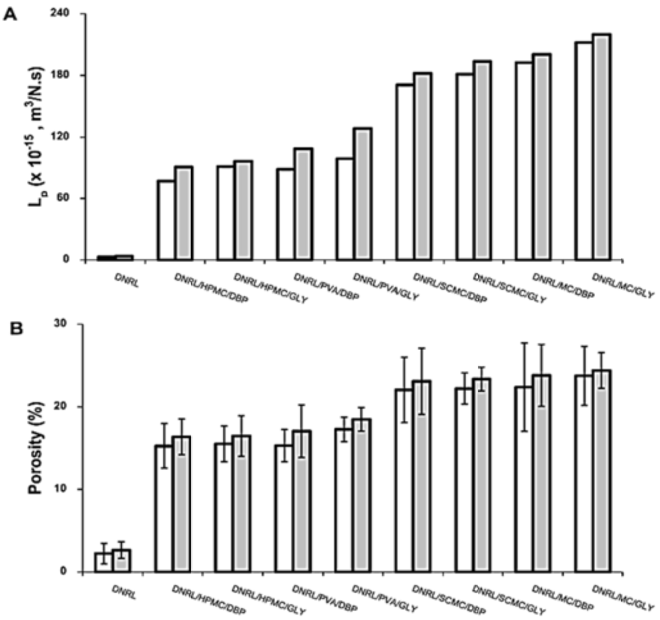

Fig. 4 (A) Hydraulic permeability and (B) percentage of porosity of natural rubber blended films (□) without and (■) nicotine loading.

However, the SCMC or MC blended films showed the very high hydraulic permeability values. These might be due to some pores from bubble air in film formation process which could be observed by SEM (data not shown). Thus, the obtained hydraulic permeability values were over-estimated.

The percentages of porosity of films determined by immersing in distilled water are shown in Fig. 4(B). The results were in the same manner. The hydrophilicity and solubility of polymers and plasticizers in natural rubber blended films were ranged in the same order. However, the SCMC or MC blended films gave not much high percentage of porosity when comparing with HPMC or PVA blends. These results were different from the hydraulic permeability values. It might be due to the effect of air bubble which acted as the big pore in films determined by hydraulic permeability technique.

However, Fig. 5 shows the relationships between hydraulic permeability and percentage of porosity values, which presented the good linearity in both without and with nicotine in blended films. Thus, the hydraulic permeability directly related to percentage of porosity values. The increasing hydraulic permeability and percentage of porosity values were observed which polymer, plasticizer, and nicotine were blended.

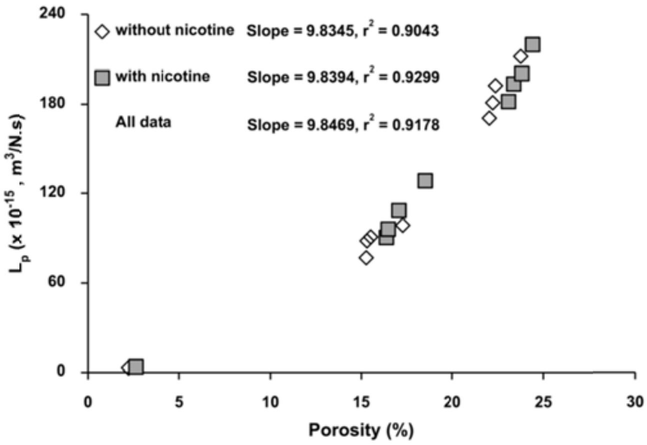

Fig. 5 Relationships between hydraulic permeability and porosity of DNRL blended films

Table 1 The relationships between hydraulic permeability and percentage of porosity values of natural rubber blended films represented as the ratio of L_P/porosity.

Formulas	Ratio of L_p/porosity	
	Without nicotine	**With nicotine**
DNRL	1.30	1.40
DNRL/HPMC/DBP	5.04	5.53
DNRL/HPMC/GLY	5.86	5.84
DNRL/PVA/DBP	5.77	6.36
DNRL/PVA/GLY	5.71	6.94
DNRL/SCMC/DBP	7.75	7.88
DNRL/SCMC/GLY	8.15	8.28
DNRL/MC/DBP	8.60	8.42
DNRL/MC/GLY	8.92	9.01

In addition, the relationships between hydraulic permeability and percentage of porosity values were evaluated, and presented as the ratio between both values which were exhibited in Table 1. It was found that there were the relationships between these values from both techniques. However, the blended polymer types, plasticizer, and nicotine could also affect the measured values due to their different properties. The DNRL membrane had the lowest ratio between hydraulic permeability and percentage of porosity in both without and with nicotine-loaded films, i.e., 1.30 and 1.40, respectively. However, this ratio increased when the hydrophilic ingredients were blended. The ratio could be separated in 3 groups; the hydrophobic DNRL film, the hydrophilic

HPMC and PVA polymer blends, and the air bubble formation SCMC and MC blends. The hydrophilic polymer blends could dissolve in water and significantly increased the water flux resulting in the high hydraulic permeability and percentage of porosity ratio when compared with DNRL alone. The air bubble formation SCMC and MC blends could act as the big way for water filtration, and the very high hydraulic permeability was obtained, resulting in the highest ratio.

Although the relationships between hydraulic permeability and percentage of porosity techniques were not unity in all natural rubber blended films, the results were in the same manner. Moreover, these results were useful for determination the hydrophilic and solubility properties of some ingredients in films, which also affected the porosity property. These properties were valuable for the prediction of drug release rate in transdermal drug delivery systems as film dosage forms. The percentage of the porosity calculated by immersing technique was quite reliable than the hydraulic permeability due to no effect of air bubble in film. However, the latter technique was easier and took less time than the first one.

Conclusions

The similar result patterns were observed in both hydraulic permeability and percentage of porosity for indicating the porosity property in natural rubber blended films. Thus, hydraulic permeability and percentage of porosity were related. However, both values were affected by blended ingredients i.e., polymers, plasticizers, and drugs in films.

Acknowledgements

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